WE CLAIM:

1. An isolated protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an isolated fragment of such protein comprising at least 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 165, 170, 171, 172, 173, or 174 contiguous amino acids having said percentages of amino acid identity compared to the corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4, wherein said protein or fragment of such protein comprises an amino acid or an amino acid sequence which corresponds to

   (a) a mutation in the mouse Agr2 protein as defined above which, if encoded by the mouse Agr2 gene and present in the genome of all or essentially all cells of a mouse in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal; and/or

   (b) a mutation in the mouse Agr2 protein or the human AGR2 protein as defined above which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

   (c) a mutation of the human AGR2 protein as defined above which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function.

2. The isolated protein or protein fragment according to claim 1, wherein said protein represents an orthologue of the mouse Agr2 or the human AGR2

protein, preferably a vertebrate orthologue, in particular an orthologue wherein said vertebrate is *Xenopus leavis*, or a mammalian orthologue, in particular an orthologue wherein said vertebrate is selected from the group consisting of a mouse, rat, rabbit, hamster, dog, cat, sheep, and horse.

3. The isolated protein or protein fragment according to claims 1 or 2, wherein said alteration results in a loss of function phenotype.

4. The isolated protein or protein fragment according to claims 1 or 2, wherein said alteration results in a gain of function phenotype.

5. The isolated protein or protein fragment according to any one of claims 1 to 4, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation and/or goblet cell mucus production or secretion and/or mucus composition.

6. The isolated protein or protein fragment according to any one of claims 1 to 3 or 5, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

7. The isolated protein or protein fragment according to any one of claims 1 to 3 or 5 to 6, wherein said phenotype is furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

8. The isolated protein or protein fragment according to any one of claims 1 to 3 or 5 to 7, wherein said alteration results in diarrhea, or diarrhea and a thriving deficit.

9. The isolated protein or protein fragment according to any one of claims 1 to 4, wherein said medical condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis,

dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

10. The isolated protein or protein fragment according to any one of claims 1 to 9, wherein said mutation results in a deletion or substitution by another amino acid of an amino acid of said mouse Agr2 protein or human AGR2 protein, or an insertion of additional amino acids not normally present in the amino acid sequence of said mouse Agr2 protein or said human AGR2 protein.

11. The isolated protein or protein fragment according to claim 10, wherein said deletion, substitution, or insertion occurs in an evolutionary conserved region of said mouse Agr2 protein or said human AGR2 protein.

12. The isolated protein or protein fragment according to claims 10 or 11, wherein said mutation results in the substitution of an amino acid which is identical or similar between mouse, rat, and human AGR2, preferably between mouse, rat, human, and *Xenopus laevis* AGR2, more preferably between mouse, rat, human, *Xenopus laevis*, and *Caenorhabditis elegans* AGR2, by another amino acid.

13. The isolated protein or protein fragment according to any one of claims 10 to 12, wherein the substitution of said amino acid of said mouse Agr2 protein or said human AGR2 protein by another amino acid is a non-conservative substitution.

14. The isolated protein or protein fragment according to any one of claims 10 to 13, wherein the amino acid of said mouse Agr2 protein or said human AGR2 protein that is deleted or substituted is Val 137.

15. The isolated protein or protein fragment according to claim 14, wherein the substitution at position 137 is one of the following substitutions:

a) Val → acidic amino acid such as Glu or Asp;

b) Val → basic amino acid, such as His, Arg or Lys;

c) Val → aliphatic hydroxyl side chain amino acid, such as Ser or Thr;

d) Val → amide side chain amino acid, such as Asn or Gln;

e) Val → sulfur containing side chain amino acid, such as Cys or Met;

f) Val → aromatic side chain amino acid, such as Phe, Tyr, Trp;

g) Val → Gly or Pro; and

h) Val → Ala, Leu or Ile.

16. The isolated protein or protein fragment according to claim 15, wherein the substitution at position 137 is a substitution of valine by glutamic acid.

17. The isolated protein or protein fragment according to any one of claims 10 to 15, wherein said amino acid is substituted by a naturally occurring amino acid.

18. An isolated protein having the amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:30, or an isolated fragment of such protein comprising at least 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 165, 170, 171, 172, 173, or 174 contiguous amino acids of said amino acid sequence, said contiguous amino acids comprising an amino acid corresponding to Glu 137.

19. A fusion protein comprising a protein or protein fragment according to any one of claims 1 to 18 fused to another protein or protein fragment not having said percentages of amino acid sequence identity to any corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4.

20. The fusion protein of claim 19, wherein said other protein is a protein unrelated to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

21. The fusion protein according to claims 19 or 20, wherein said other protein is selected from the group consisting of glutathione-S-transferase, an immunoglobulin peptide, a polyhistidine peptide, a FLAG tag, and streptavidin.

22. An isolated nucleic acid encoding a protein or a fragment of such protein according to any one of claims 1 to 18, or an isolated nucleic acid which is complementary thereto.

23. An isolated nucleic acid having the nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:29, or an isolated nucleic acid which is complementary thereto.

24. An episomal element comprising a nucleic acid as defined in any one of claims 22 or 23.

25. The episomal element according to claim 24, wherein said episomal element is selected from a plasmid, a cosmid, a bacterial phage nucleic acid, or a viral nucleic acid.

26. A genome comprising a nucleic acid as defined in any one of claims 22 or 23.

27. The genome according to claim 26, wherein said genome is a bacteriophage genome, a bacteria genome, or a virus genome.

28. The genome of claim 27, wherein said virus genome is a DNA viral genome or an RNA viral genome.

29. A vector comprising a nucleic acid molecule encoding the protein according to any one of claims 1 to 21.

30. The vector according to claim 29, wherein said vector is selected from the group consisting of an expression vector, a mutagenesis vector, an integration vector and a mutation vector.

31. The vector according to claim 30, wherein said vector is an expression vector and wherein the sequence encoding said protein is operably linked to a promoter sequence.

32. The vector according to claims 30 or 31, wherein said vector is an expression vector and is selected from the group consisting of a plasmid vector, a cosmid vector, a phage vector, a phagemid vector, a viral vector, and a retroviral vector.

33. A host cell transfected with the episomal element, genome, or vector of any one of claims 24 to 32.

34. The host cell according to claim 33, wherein said host cell is a eukaryotic cell.

35. The host cell according to claim 33, wherein said host cell is a prokaryotic cell.

36. An antisense nucleic acid comprising a nucleotide sequence which is complementary to

(i) a part of an mRNA encoding a protein according to any one of claims 1 to 21, said part encoding an amino acid sequence comprising the amino acid or amino acid sequence which corresponds to

(a) the mutation in the mouse Agr2 protein according to SEQ ID NO:3 which, if encoded by the mouse Agr2 gene and present in the genome of all or essentially all cells of a mouse in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function

compared to the corresponding wild-type animal, said phenotype optionally being furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland; and/or

(b) the mutation in the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

(c) the mutation of the human AGR2 protein according to SEQ ID NO:4 which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function;

(ii) a part of the mRNA encoding the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein as defined above, said part being a non-coding part and comprising a sequence corresponding to a mutation in the gene coding for said protein or orthologue which affects expression of said protein or orthologue; or

(iii) a part of the mRNA encoding a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%,

98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

37. The antisense nucleic acid of claim 36, wherein said antisense nucleic acid is selected from the group consisting of DNA, RNA, and a synthetic nucleic acid analog, such as a PNA (peptide nucleic acid).

38. The antisense nucleic acid of claims 36 or 37, wherein said antisense nucleic acid is capable of hybridizing to said mRNA via said complementary nucleotide sequence under physiological conditions, or under conditions of high stringency, preferably under hybridization conditions of a high salt buffer comprising 6x SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2x SSC, 0.01% BSA at 50°C, furthermore preferably under hybridization conditions of a high salt buffer comprising 6x SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2x SSC, 0.01% BSA at 65°C.

39. The antisense nucleic acid of any one of claims 36 to 38, wherein said antisense nucleic acid is a ribozyme and further comprises a catalytic region.

40. The antisense nucleic acid according to claim 39, wherein said catalytic region is capable of cleaving said mRNA.

41. The antisense nucleic acid of any one of claims 38 to 40, wherein said hybridization to said mRNA is more effective than hybridization to

(i) the mRNA encoding the same protein which, however, corresponds to the wild-type mouse Agr2 or human AGR2 protein according to

SEQ ID NO:3 and SEQ ID NO:4 in respect of said amino acid sequence;

(ii) the mRNA encoded by the wild-type gene of the mouse Agr2 or human AGR2 protein as defined above, or the wild-type gene of the corresponding orthologue; or

(iii) the mRNA encoded by the wild-type gene of the corresponding protein which affects expression or function of the mouse Agr2 or the human AGR2 protein as defined above.

42. A host cell transformed with an antisense nucleic acid according to any one of claims 36 to 41.

43. The host cell according to claim 42, wherein said host cell is a eukaryotic cell.

44. The host cell according to claim 42, wherein said host cell is a prokaryotic cell.

45. A short interfering RNA (siRNA) comprising a double stranded nucleotide sequence wherein one strand is complementary to an at least 19, 20, 21, 22, 23, 24, or 25 nucleotide long segment of an mRNA encoding

(a) the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or

(b) a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

46. The siRNA of claim 45, wherein said siRNA is capable of silencing or suppressing the expression of the AGR2 gene encoding said mRNA.

47. The siRNA of claims 45 or 46, wherein said AGR2 gene is a vertebrate AGR2 gene, in particular a *Xenopus leavis* AGR2 gene, or a mammalian AGR2 gene, in particular an AGR2 gene selected from the group consisting of the AGR2 gene of human, mouse, rat, rabbit, hamster, dog, cat, sheep, and horse, most preferably a mouse Agr2 gene or a human AGR2 gene.

48. The siRNA of any one of claims 45 to 47, wherein said AGR2 gene is an AGR2 gene of a human subject unaffected by or known not to be at risk of developing a condition associated with an alteration in goblet cell function.

49. A short interfering RNA (siRNA) comprising a double stranded nucleotide sequence wherein one strand is complementary to an at least 19, 20, 21, 22, 23, 24, or 25 nucleotide long segment of an mRNA encoding

(i) a protein according to any one of claims 1 to 21, said segment encoding an amino acid sequence comprising the amino acid or amino acid sequence which corresponds to

(a) the mutation in the mouse Agr2 protein according to SEQ ID NO:3 which, if encoded by the mouse Agr2 gene and present in the genome of all or essentially all cells of a mouse in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal, said phenotype optionally being furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland; and/or

(b) the mutation in the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, which leads to an altered biological activity of

the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

(c) the mutation of the human AGR2 protein according to SEQ ID NO:4 which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function;

(ii) the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein as defined above, said segment being a non-coding segment and comprising a sequence corresponding to a mutation in the gene coding for said protein or orthologue which affects expression of said protein or orthologue; or

(iii) a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

50. The siRNA according to any one of claims 45 to 49, wherein said segment includes sequences from the 5' untranslated (UT) region, the open reading frame (ORF), or the 3' UT region of said mRNA.

51. A host cell transformed with an siRNA according to any one of claims 45 to 50.

52. The host cell according to claim 51, wherein said host cell is a eukaryotic cell.

53. The host cell according to claim 51, wherein said host cell is a prokaryotic cell.

54. An antibody specifically recognizing an epitope in a protein according to any one of claims 1 to 21, wherein said epitope comprises the amino acid or the amino acid sequence in said protein which corresponds to

(a) the mutation in the mouse Agr2 protein according to SEQ ID NO:3 which, if encoded by the mouse Agr2 gene and present in the genome of all or essentially all cells of a mouse in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal, said phenotype optionally being furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland; and/or

(b) the mutation in the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

(c) the mutation of the human AGR2 protein according to SEQ ID NO:4 which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration

in goblet cell function with altered AGR2 expression or function; and/or

(d) Glu 137 in SEQ ID NO:2 and SEQ ID NO:30.

55. The antibody according to claim 54, wherein said antibody is a high affinity antibody.

56. The antibody according to claims 54 or 55, wherein the antibody is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a single-chain antibody, and an F_{ab}, $F_{ab'}$, or $F_{(ab')2}$ fragment.

57. The antibody according to any one of claims 54 to 56, wherein said antibody is of a class selected from IgG, IgM, IgA, IgE, and IgD.

58. The antibody according to claim 57, wherein said antibody is of the class IgG_1 or IgG_2.

59. The antibody according to any one of claims 54 to 58, wherein said antibody is a humanized antibody or a human antibody.

60. The antibody according to any one of claims 54 to 59, wherein said antibody is a bispecific antibody, preferably an antibody wherein one of the binding specificities is for said epitope and the other binding specificity is for a cell-surface protein, such as a cell surface receptor or a cell surface receptor subunit.

61. The antibody according to any one of claims 54 to 59, wherein said antibody is covalently joined to another antibody to form a heteroconjugate antibody.

62. The antibody according to any one of claims 54 to 61, wherein said antibody is modified regarding its effector function.

63. An immunoconjugate comprising an antibody according to any one of claims 54 to 62 conjugated to

(a) a cytotoxic agent;

(b) a receptor or ligand capable of interacting with a cytotoxic agent or with a ligand or receptor bound to a cytotoxic agent; or

(c) to an imaging agent.

64. The immunoconjugate according to claim 63, wherein the cytotoxic agent is selected from a chemotherapeutic agent, a toxin, or a radioactive isotope.

65. The immunoconjugate according to claims 63 or 64, wherein said receptor is streptavidin and said ligand bound to the cytotoxic agent is avidin.

66. The immunoconjugate according to claim 63, wherein the imaging agent is a radioactive isotope, preferably a radioactive isotope selected from ^{18}F, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, ^{131}I, ^{169}Yb, ^{186}Re, and ^{201}Tl, preferably ^{99m}Tc.

67. The immunoconjugate according to claim 63 or 66, wherein said imaging agent is complexed to a chelating group which is covalently attached to the antibody.

68. An anticalin specifically binding an epitope in a protein according to any one of claims 1 to 21, wherein said epitope comprises the amino acid or the amino acid sequence in said protein which corresponds to

(a) the mutation in the mouse Agr2 protein according to SEQ ID NO:3 which, if encoded by the mouse Agr2 gene and present in the genome of all or essentially all cells of a mouse in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal, said phenotype optionally being furthermore associated

with an increased proliferation of the glandular epithelium of the Brunner's gland; and/or

(b) the mutation in the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

(c) the mutation of the human AGR2 protein according to SEQ ID NO:4 which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function; and/or

(d) Glu 137 in SEQ ID NO:2 and SEQ ID NO:30.

69. An anticalin specifically binding an epitope in a protein which corresponds to

(a) the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or

(b) a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

70. An aptamer specifically binding an epitope in a protein according to any one of claims 1 to 21, wherein said epitope comprises the amino acid or the amino acid sequence in said protein which corresponds to

(a) the mutation in the mouse Agr2 protein according to SEQ ID NO:3 which, if encoded by the mouse Agr2 gene and present in the genome of all or essentially all cells of a mouse in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal, said phenotype optionally being furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland; and/or

(b) the mutation in the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

(c) the mutation of the human AGR2 protein according to SEQ ID NO:4 which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function; and/or

(d) Glu 137 in SEQ ID NO:2 and SEQ ID NO:30.

71. An aptamer specifically binding an epitope in a protein which corresponds to

(a) the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof

having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or

(b) a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

72. A non-human vertebrate animal comprising in the genome of at least some of its cells an allele of a gene encoding a protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, said allele comprising a mutation which,

a) if present in the genome of all or essentially all cells of said animal in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal; and/or

b) corresponds to a mutation in the mouse Agr2 protein or the human AGR2 protein as defined above which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

c) corresponds to a mutation of the human AGR2 protein as defined above which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function.

73. A non-human vertebrate animal comprising in the genome of at least some of its cells an allele of a gene coding for a protein which affects expression or function of the AGR2 protein of said animal, said allele comprising a mutation which, if present in the genome of all or essentially all cells of said animal in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal.

74. The animal according to claims 72 or 73, wherein said alteration results in a loss of function phenotype.

75. The animal according to claims 72 or 73, wherein said alteration results in a gain of function phenotype.

76. The animal according to any one of claims 72 to 75, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation, and/or goblet cell mucus production or secretion and/or mucus composition.

77. The animal according to any one of claims 72 to 74, or 76, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, and secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

78. The animal according to any one of claims 72 to 74 or 76 to 77, wherein said phenotype is furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

79. The animal according to any one of claims 72 to 74, or 76 to 78, wherein said alteration results in diarrhea, or diarrhea and a thriving deficit.

80. The animal according to any one of claims 72 to 79, wherein said gene is an endogenous gene with respect to said animal.

81. The animal according to any one of claims 72 or 74 to 80, wherein said gene encodes a protein which is an orthologue of SEQ ID NO:3 and SEQ ID NO:4 with respect to said animal.

82. The animal according to any one of claims 72 to 79, wherein said gene is a heterologous gene with respect to said animal.

83. The animal according to any one of claims 72 or 74 to 82 wherein said gene encodes a protein according to any one of claims 1 to 18.

84. The animal according to claim 83 wherein said gene encodes a protein having the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:30.

85. The animal according to any one of claims 72 to 84, wherein said animal is a transgenic animal.

86. The animal according to any one of claims 72 to 85, wherein said mutation results in the reduction or complete abolishment of expression of said gene.

87. The animal according to any one of claims 72 to 86, wherein said allele is expressed under the control of a promoter other than the endogenous promoter of said gene.

88. The animal according to claim 87, wherein said promoter has a tissue specificity other than that of the endogenous promoter of said gene.

89. The animal according to claims 87 or 88, wherein said promoter is an inducible promoter.

90. The animal according to any one of claims 72 to 89, wherein said cells are the germ cells of said animal.

91. The animal according to any one of claims 72 to 89, wherein said cells are the somatic cells of said animal.

92. The animal according to claims 90 or 91, wherein the genome of all or essentially all of the germ cells and the somatic cells of said animal comprise said allele.

93. The animal according to any one of claims 72 to 92, wherein said genome of said cells is homozygous in respect of said allele.

94. The animal according to any one of claims 72 to 93, wherein said animal is a mammalian animal, preferably a rodent.

95. The animal according to claim 94, wherein said animal is selected from the group consisting of a mouse, rat, rabbit, hamster, dog, cat, sheep, and horse.

96. Use of the non-human vertebrate animal according to any one of claims 72 to 95 for the identification of a protein or nucleic acid diagnostic marker for a goblet cell-related disorder, or as an animal model for studying the molecular mechanisms of, or physiological processes associated with, a goblet cell-related disorder, or for the identification and testing of an agent useful in the prevention, amelioration, or treatment of a goblet cell-related disorder.

97. The use according to claim 96, wherein said goblet cell-related disorder is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

98. Use of the non-human vertebrate animal according to any one of claims 72 to 95 for studying the molecular mechanisms of, or physiological processes associated with, conditions associated with, or affected by, reduced activity or undesirable, e.g. increased, activity of endogenous AGR2; reduced expression, reduced production or undesirable, e.g. increased, production of endogenous AGR2; or for the identification and testing of an agent useful in the prevention, amelioration, or treatment of these conditions.

99. The uses according to any one of claims 96 to 98, wherein said agent is selected from the group consisting of a small molecule drug, a (poly)peptide, and a nucleic acid.

100. The use of claim 99, wherein said agent is an antagonist of AGR2.

101. The use of claim 99, wherein said agent is an agonist of AGR2.

102. Use of the non-human vertebrate animal according to any one of claims 72 to 95 for studying or identifying protein or nucleic acid diagnostic markers, such as an early gene diagnostic marker, for diseases associated with AGR2 deficiency or over-expression.

103. Use of the non-human vertebrate animal according to any one of claims 72 to 95 for identifying receptors of the AGR2 protein, or genes or proteins regulated by AGR2 activity and deregulated in disorders associated with AGR2 deficiency or overexpression.

104. A method of identifying a protein or nucleic acid marker indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, said method comprising the step of analyzing a test sample derived from a human subject for the presence of a difference compared to a similar test sample if

derived from a human subject unaffected by or known not to be at risk of developing said condition, wherein said difference is indicative of the presence of a mutation in an allele of the gene coding for the AGR2 protein according to SEQ ID NO:4, or in an allele of a gene coding for a protein which affects expression or function of said AGR2 protein.

105. A method of identifying a protein or nucleic acid marker indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function, said method comprising the step of analyzing a test sample derived from a human subject for the presence of a difference compared to a similar test sample if derived from a human subject unaffected by or known not to be at risk of developing said condition, wherein said difference is indicative of the presence of a mutation in an allele of the gene coding for the AGR2 protein according to SEQ ID NO:4, or in an allele of a gene coding for a protein which affects expression or function of said AGR2 protein.

106. The method of claims 104 or 105, wherein said test sample is analyzed for a difference compared to similar test samples if derived from a group of human subjects unaffected by, or known not to be at risk of developing, said condition.

107. The method according to any one of claims 104 to 106, wherein said human subject whose test sample is analyzed has a condition or is known or suspected to be at risk of developing a condition associated with an alteration in goblet cell function.

108. The method of any one of claims 104 to 107, further comprising the step of obtaining said similar test sample or said similar test samples from said human subject or group of human subjects unaffected by, or known not to be at risk of developing, said condition.

109. The method according to any one of claims 104 to 108, wherein said alteration results in a loss of function phenotype.

110. The method according to any one of claims 104 to 108, wherein said alteration results in a gain of function phenotype.

111. The method according to any one of claims 104 to 110, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation, and/or goblet cell mucus production or secretion and/or mucus composition.

112. The method according to any one of claims 104 to 109 or 111, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, and secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

113. The method according to any one of claims 104 to 109 or 111 to 112, wherein said medical condition is furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

114. The method according to any one of claims 104 to 109 or 111 to 113, wherein said alteration results in diarrhea.

115. The method according to any one of claims 104 to 110, wherein said medical condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

116. The method according to any one of claims 104 to 115, wherein said test sample is a nucleic acid sample.

117. The method according to claim 116, wherein said nucleic acid is selected from the group consisting of mRNA and genomic DNA.

118. The method according to claims 116 or 117, wherein the step of analyzing said nucleic acid sample comprises amplifying at least a portion of its nucleic acid via the polymerase chain reaction, and optionally also amplifying via the polymerase chain reaction at least a portion of the nucleic acid of said similar sample or said similar samples.

119. The method according to any one of claims 104 to 115, wherein said test sample is a protein sample.

120. The method according to claim 119, wherein said protein is the AGR2 protein.

121. The method according to claims 116 to 120, wherein said difference is one in the expression level of said nucleic acid or said protein.

122. The method according to claims 116 to 120, wherein said difference is one in the nucleotide or amino acid sequence of said nucleic acid or said protein.

123. The method according to claim 122, wherein the step of analyzing comprises the partial or complete determination of the sequence of the nucleic acid or the amplified portion of the nucleic acid of said sample, and optionally also of the nucleic acid or the amplified portion of the nucleic acid of said similar sample or said similar samples.

124. The method according to any one of claims 104 to 123, wherein said allele is comprised in the genome of the germ cells of said human subject.

125. The method according to any one of claims 104 to 123, wherein said allele is comprised in the genome of the somatic cells of said human subject.

126. The method according to claims 124 or 125, further comprising the step of determining whether the genome of said germ cells or said somatic cells is homozygous with respect to said mutation in said allele.

127. The method according to any one of claims 104 to 126, wherein said mutation results in a deletion or substitution by another amino acid of an amino acid of the AGR2 protein encoded by said allele, or an insertion of additional amino acids not normally present in the amino acid sequence of the AGR2 protein according to SEQ ID NO:4.

128. The method according to claim 127, wherein said deletion, substitution, or insertion occurs in an evolutionary conserved region of said AGR2 protein.

129. The method according to claims 127 or 128, wherein said mutation results in the substitution of an amino acid which is identical or similar between mouse, rat, and human AGR2, preferably between mouse, rat, human, and *Xenopus laevis* AGR2, more preferably between mouse, rat, human, *Xenopus laevis*, and *Caenorhabditis elegans* AGR2, by another amino acid.

130. The method according to any one of claims 127 to 129, wherein the substitution of said amino acid of the AGR2 protein by another amino acid is a non-conservative substitution.

131. The method according to any one of claims 127 to 130, wherein said amino acid of the AGR2 protein that is deleted or substituted is Val 137.

132. The method according to claim 131, wherein the substitution at position 137 is one of the following substitutions:

a) Val → acidic amino acid such as Glu or Asp;

b) Val → basic amino acid, such as His, Arg or Lys;

c) Val → aliphatic hydroxyl side chain amino acid, such as Ser or Thr;

d) Val → amide side chain amino acid, such as Asn or Gln;

e) Val → sulfur containing side chain amino acid, such as Cys or Met;

f) Val → aromatic side chain amino acid, such as Phe, Tyr, Trp;

g) Val → Gly or Pro; and

h) Val → Ala, Leu or Ile.

133. The method according to claim 132, wherein the substitution at position 137 is a substitution of valine by glutamic acid.

134. The method according to any one of claims 127 to 132, wherein said amino acid is substituted by a naturally occurring amino acid.

135. A method for identifying a predisposition of a human subject for developing a medical condition associated with an alteration in goblet cell function, said method comprising the step of determining whether a test sample derived from said human subject indicates the presence of a mutation in an allele of the gene coding for the AGR2 protein according to SEQ ID NO:4 indicative of an increased risk of said human subject of developing said medical condition.

136. The method according to claim 135, further comprising the step of assigning a certain risk of developing said medical condition to said human subject.

137. A method for determining whether a medical condition in a human subject which is associated with an alteration in goblet cell function is associated with altered AGR2 expression or function, said method comprising the step of determining whether a test sample derived from said human subject indicates the presence of a mutation in an allele of the gene coding for the AGR2 protein according to SEQ ID NO:4 indicative of an altered AGR2 expression or function.

138. The method according to claim 137, further comprising the step of assigning an association with altered AGR2 expression or function to said human subject's medical condition.

139. The method according to any one of claims 135 to 138, wherein said alteration results in a loss of function phenotype.

140. The method according to any one of claims 135 to 138, wherein said alteration results in a gain of function phenotype.

141. The method according to any one of claims 135 to 140, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation, and/or goblet cell mucus production or secretion and/or mucus composition.

142. The method according to any one of claims 135 to 139 or 141, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, and secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

143. The method according to any one of claims 135 to 139 or 141 to 142, wherein said medical condition is furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

144. The method according to any one of claims 135 to 139 or 141 to 143, wherein said alteration results in diarrhea.

145. The method according to any one of claims 135 to 140, wherein said medical condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

146. The method according to any one of claims 135 to 145 wherein said test sample is a nucleic acid sample.

147. The method according to claim 146, wherein said nucleic acid is selected from the group consisting of mRNA and genomic DNA.

148. The method according to any one of claims 135 to 145, wherein said test sample is a protein sample.

149. The method according to claim 148, wherein said protein is the AGR2 protein.

150. The method according to any one of claims 135 to 149, wherein said allele is comprised in the genome of the germ cells of said human subject.

151. The method according to any one of claims 135 to 149, wherein said allele is comprised in the genome of the somatic cells of said human subject.

152. The method according to claims 150 or 151, further comprising the step of determining whether the genome of said germ cells or said somatic cells is homozygous with respect to said mutation in said allele.

153. The method according to any one of claims 135 to 152, wherein said mutation results in the reduction or complete abolishment of expression of the AGR2 protein.

154. The method according to any one of claims 135 to 153, wherein said mutation results in a deletion or substitution by another amino acid of an amino acid of the AGR2 protein encoded by said allele, or an insertion of additional amino acids not normally present in the amino acid sequence of the AGR2 protein according to SEQ ID NO:4.

155. The method according to claim 154, wherein said deletion, substitution, or insertion occurs in an evolutionary conserved region of said AGR2 protein.

156. The method according to claims 154 or 155, wherein said mutation results in the substitution of an amino acid which is identical or similar between mouse, rat, and human AGR2, preferably between mouse, rat, human, and *Xenopus laevis* AGR2, more preferably between mouse, rat, human, *Xenopus laevis*, and *Caenorhabditis elegans* AGR2, by another amino acid.

157. The method according to any one of claims 154 to 156, wherein the substitution of said amino acid of the AGR2 protein by another amino acid is a non-conservative substitution.

158. The method according to any one of claims 154 to 157, wherein said amino acid of the AGR2 protein that is deleted or substituted is Val 137.

159. The method according to claim 158, wherein the substitution at position 137 is one of the following substitutions:

a) Val → acidic amino acid such as Glu or Asp;
b) Val → basic amino acid, such as His, Arg or Lys;
c) Val → aliphatic hydroxyl side chain amino acid, such as Ser or Thr;
d) Val → amide side chain amino acid, such as Asn or Gln;
e) Val → sulfur containing side chain amino acid, such as Cys or Met;
f) Val → aromatic side chain amino acid, such as Phe, Tyr, Trp;
g) Val → Gly or Pro; and
h) Val → Ala, Leu or Ile.

160. The method according to claim 159, wherein the substitution at position 137 is a substitution of valine by glutamic acid.

161. The method according to any one of claims 154 to 159, wherein said amino acid is substituted by a naturally occurring amino acid.

162. The method according to any one of claims 135 to 152 and 154 to 161, wherein said gene codes for a AGR2 protein having the sequence set forth in SEQ ID NO:30.

163. A pharmaceutical composition comprising a protein or protein fragment according to any one of claims 1 to 21, a nucleic acid according to claim 22 or 23, an episomal element or vector according to any one of claims 24, 25, and 29 to 32, an antisense nucleic acid according to any one of claims 36 to 41, an siRNA according to any one of claims 45 to 50, an antibody according to any one of claims 54 to 62, an immunoconjugate according to any one of claims 63 to 67, an anticalin according to claims 68 or 69, or an aptamer according to claims 70 or 71, and a pharmaceutically acceptable carrier.

164. The protein or protein fragment according to any one of claims 1 to 21, the nucleic acid according to claim 22 or 23, the episomal element or vector according to any one of claims 24, 25, and 29 to 32, the antisense nucleic acid according to any one of claims 36 to 41, the siRNA according to any one of claims 45 to 50, the antibody according to any one of claims 54 to 62, the immunoconjugate according to any one of claims 63 to 67, the anticalin according to claims 68 or 69, or the aptamer according to claims 70 or 71 for use as a medicament.

165. The protein or protein fragment, nucleic acid, episomal element, vector, antisense nucleic acid, siRNA, antibody, aptamer, anticalin, or immunoconjugate according to claim 164 for the use specified therein, wherein the medicament is for treating a medical condition in a human subject which is associated with an alteration in goblet cell function, said medical condition optionally being furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

166. The protein or protein fragment, nucleic acid, episomal element, vector, antisense nucleic acid, siRNA, antibody, aptamer, anticalin, or immunoconjugate according to claim 165 for the use specified therein, wherein said alteration is an alteration in goblet cell differentiation and/or goblet cell mucus production or secretion and/or mucus composition.

167. The protein or protein fragment, nucleic acid, episomal element, vector, antisense nucleic acid, siRNA, antibody, aptamer, anticalin, or immunoconjugate according to claim 165 or 166 for the use specified therein, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, and secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

168. The protein or protein fragment, nucleic acid, episomal element, vector, antisense nucleic acid, siRNA, antibody, aptamer, anticalin, or immunoconjugate according to any one of claims 165 to 167, wherein said alteration results in diarrhea.

169. The protein or protein fragment, nucleic acid, episomal element, vector, antisense nucleic acid, siRNA, antibody, aptamer, anticalin, or immunoconjugate according to claims 164 or 165 for the use specified therein, wherein said medicament is for treating a condition selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

170. A method of producing a mutant AGR2 protein comprising culturing a host cell according to any one of claims 33 to 35 in a suitable medium under conditions such that the protein is expressed, and harvesting the cells or the medium.

171. The method according to claim 170, wherein the protein is subsequently further purified from said cells or said medium.

172. A method of gene therapy comprising delivering to cells in a human subject suffering from or known to be at risk of developing a condition associated with an alteration in goblet cell function a DNA construct comprising

(a) a sequence of an allele of the AGR2 gene encoding the human AGR2 protein according to SEQ ID NO:4, or encoding a protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or a sequence of an allele of the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition;

(b) a DNA sequence encoding the human AGR2 protein according to SEQ ID NO:4, or a human AGR2 protein encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition, or a protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively;

(c) a DNA sequence encoding an antisense nucleic acid according to any one of claims 36 to 41, or an antisense nucleic acid comprising a nucleotide sequence which is complementary to an mRNA encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition;

(d) a DNA sequence encoding an siRNA according to any one of claims 45 to 50;

(e) a DNA sequence encoding an aptamer according to any one of claims 70 to 71; or

(f) a DNA sequence encoding an AGR2 protein according to any one of claims 1 to 21.

173. The method of claim 172, wherein said human AGR2 gene of a subject unaffected by or known not to be at risk of developing said condition is a gene encoding a human AGR2 protein according to SEQ ID NO:4.

174. The method of claims 172 or 173, wherein said cells are intestinal cells of said human subject, preferably goblet cells.

175. The method of claims 172 or 173, wherein said cells are gastrointestinal cells of said human subject, preferably goblet cells and/or mucus secreting cells of the Brunner's gland.

176. The method of claims 172 or 173, wherein said cells are cells of the respiratory tract of said human subject, preferably goblet cells and/or mucus secreting cells of the submucosal glands of the trachea.

177. The method of any one of claims 172 to 176, wherein the DNA construct is a viral vector.

178. The method of any one of claims 172 to 177, wherein said DNA construct is capable of directing expression of said protein, said antisense nucleic acid, or said siRNA.

179. The method of claim 178, wherein said expression is transient.

180. The method of any one of claims 172 to 178, wherein the DNA construct is capable of being stably integrated into the genome of said cells.

181. The method of any one of claims 172 to 180, wherein said sequence of an allele of the AGR2 gene comprises coding sequences of said gene.

182. The method of any one of claims 172 to 181, wherein said sequence of an allele of the AGR2 gene comprises non-coding sequences of said gene.

183. Use of a DNA construct comprising

(a) a sequence of an allele of the AGR2 gene encoding the human AGR2 protein according to SEQ ID NO:4, or encoding a protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or a sequence of an allele of the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition;

(b) a DNA sequence encoding the human AGR2 protein according to SEQ ID NO:4, or a human AGR2 protein encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition, or a protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively;

(c) a DNA sequence encoding an antisense nucleic acid according to any one of claims 36 to 41, or an antisense nucleic acid comprising a nucleotide sequence which is complementary to an mRNA encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition;

(d) a DNA sequence encoding an siRNA according to any one of claims 45 to 50;

(e) a DNA sequence encoding an aptamer according to any one of claims 70 to 71; or

(f) a DNA sequence encoding an AGR2 protein according to any one of claims 1 to 21

for the preparation of a pharmaceutical for the treatment of a condition associated with an alteration in goblet cell function, said condition optionally being furthermore associated with an increased proliferation of

the glandular epithelium of the Brunner's gland, or the prevention of said condition in a human subject known to be at risk of developing such condition.

184. A method of preventing, treating, or ameliorating a medical condition in a human subject associated with an alteration in goblet cell function, said method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject.

185. The method of claim 184, wherein said pharmaceutical composition is a pharmaceutical composition according to claim 163.

186. The method according to claim 184, wherein said agent capable of modulating AGR2 activity in said human subject is

(a) an isolated protein having the sequence of the human AGR2 protein according to SEQ ID NO:4,

(b) an isolated protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, wherein said protein shows the same or essentially the same activity as the human AGR2 protein according to SEQ ID NO:4 in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay;

(c) an isolated fragment of the protein according to (a) or (b) above comprising at least 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 165, 170, 171, 172, 173, or 174 contiguous amino acids having said percentages of amino acid identity compared to the corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4, wherein said fragment shows the same or essentially the same activity as the human AGR2 protein according

to SEQ ID NO:4 in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay;

(d) a fusion protein comprising a protein or protein fragment according to (a) to (c) above fused to another protein or protein fragment not having said percentages of amino acid sequence identity to any corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4; preferably fused to a protein unrelated to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively;

(e) an antibody specifically recognizing an epitope comprised within the human AGR2 protein according to SEQ ID NO:4, or within a human AGR2 protein encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing a medical condition associated with altered goblet cell function; or

(f) an antisense nucleic acid comprising a nucleotide sequence which is complementary to an mRNA encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition, preferably encoded by the AGR2 gene encoding the human AGR2 protein according to SEQ ID NO:4.

187. Use of an agent capable of modulating AGR2 activity for the preparation of a pharmaceutical for preventing, treating, or ameliorating a medical condition in a human subject associated with an alteration in goblet cell function, said condition optionally being furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

188. The use according to claim 187, wherein said agent is selected from the group consisting of a protein or protein fragment according to any one of claims 1 to 21, a nucleic acid according to claim 22 or 23, an episomal element or vector according to any one of claims 24, 25, and 29 to 32, an antisense nucleic acid according to any one of claims 36 to 41, an siRNA

according to any one of claims 45 to 50, an antibody according to any one of claims 54 to 62, an immunoconjugate according to any one of claims 63 to 67, an anticalin according to claims 68 or 69, and an aptamer according to claims 70 or 71.

189. The use according to claim 187, wherein said agent capable of modulating AGR2 activity in said human subject is

(a) an isolated protein having the sequence of the human AGR2 protein according to SEQ ID NO:4,

(b) an isolated protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, wherein said protein shows the same or essentially the same activity as the human AGR2 protein according to SEQ ID NO:4 in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay;

(c) an isolated fragment of the protein according to (a) or (b) above comprising at least 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 165, 170, 171, 172, 173, or 174 contiguous amino acids having said percentages of amino acid identity compared to the corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4, wherein said fragment shows the same or essentially the same activity as the human AGR2 protein according to SEQ ID NO:4 in an *in vitro* assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay;

(d) a fusion protein comprising a protein or protein fragment according to (a) to (c) above fused to another protein or protein fragment not having said percentages of amino acid sequence identity to any corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4;

preferably fused to a protein unrelated to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively;

(e) an antibody specifically recognizing an epitope comprised within the human AGR2 protein according to SEQ ID NO:4, or within a human AGR2 protein encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing a medical condition associated with altered goblet cell function; or

(f) an antisense nucleic acid comprising a nucleotide sequence which is complementary to an mRNA encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition, preferably encoded by the AGR2 gene encoding the human AGR2 protein according to SEQ ID NO:4.

190. Use of a wild type AGR2 protein, e.g., an AGR2 wild type protein according to SEQ ID NO:4, a nucleic acid encoding such a protein, e.g., a nucleic acid having the nucleotide sequence set forth in SEQ ID NO: 5, or a small molecule agonist of AGR2 for preventing, treating, or ameliorating a medical condition in a human subject associated with an alteration in goblet cell function, where the medical condition is selected from the group consisting of dry eye syndrome, gastric disease, peptic ulcer inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

191. Use of a small molecule antagonist of AGR2 for preventing, treating, or ameliorating a medical condition in a human subject associated with an alteration in goblet cell function, where the medical condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis.

192. A method of identifying an agent useful in the prevention, amelioration, or treatment of a goblet cell-related disorder, the method comprising

a) culturing mammalian goblet cells in the presence or absence of a candidate agent; and

b) determining whether the presence of the agent results in an increase in the production by the cells of mucus and/or one or more particular mucus constituents;

wherein said goblet cells show a reduced or no expression of the AGR2 protein, or carry a mutation in one or both alleles of their endogenous AGR2 gene so that the allele is no longer capable of being expressed, or that it encodes a protein according to any one of claims 1 to 18.

193. A method of identifying an agent useful in the prevention, amelioration, or treatment of a goblet cell-related disorder, the method comprising

a) culturing mammalian goblet cells in the presence or absence of a candidate agent; and

b) determining whether the presence of the agent results in a decrease in the production by the cells of mucus and/or one or more particular mucus constituents;

wherein said goblet cells show an increased expression of the AGR2 protein, or carry a mutation in one or both alleles of their endogenous AGR2 gene so that the allele shows an increased amount of expression or that it encodes a protein according to any one of claims 1 to 18.

194. A method of identifying an antagonist of the AGR2 protein, the method comprising

a) culturing mammalian goblet cells in the presence or absence of a wild-type mammalian AGR2 protein, preferably the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; and

b) determining whether an increase in the production by the cells of mucus and/or one or more particular mucus constituents in the presence of said wild-type AGR2 protein is observed upon the addition of a candidate antagonist agent to the cultured cells.

195. A method of identifying an antagonist of the AGR2 protein, the method comprising

a) culturing mammalian goblet cells in the presence or absence of a wild-type mammalian AGR2 protein, preferably the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; and

b) determining whether a decrease in the production of mucus and/or one or more particular mucus constituents by the cells which are cultured in the presence of the wild-type mammalian AGR2 protein is observed upon the addition of a candidate antagonist agent to the cultured cells.

196. The method according to claims 194 or 195, wherein said goblet cells show a reduced or no expression of the AGR2 protein, or carry a mutation in one or both alleles of their endogenous AGR2 gene so that the allele is no longer capable of being expressed or that it encodes a protein according to any one of claims 1 to 18.

197. The method according to claim 192, 193 or 196, wherein said cells are homozygous for said mutated endogenous AGR2 allele.

198. The method according to any one of claims 192, 196 or 197, wherein said cells do not additionally contain a functional allele of a wild type AGR2 gene (i.e., no functional allele of the corresponding wild type orthologue, or of a heterologous wild type AGR2 gene), or a nucleic acid sequence expressing a wild type AGR2 protein (representing either the corresponding wild type orthologue, or a heterologous wild type AGR2 protein).

199. The method according to any one of claims 192, 193 and 196 to 198, wherein said protein encoded by said mutated allele has the amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:30.

200. The method according to any one of claims 192 to 199, wherein the mucus constituent is mucin2 or a trefoil peptide.

201. The method according to claim 200, wherein it is determined whether the presence of the agent results in an increase in the production of both mucin2 and one or more of the trefoil peptides, or whether an increase in the production of both mucin2 and one or more of the trefoil peptides in the presence of said wild-type AGR2 protein is observed upon the addition of said candidate antagonist agent.

202. The method according to claim 200, wherein it is determined whether the presence of the agent results in a decrease in the production of both mucin2 and one or more of the trefoil peptides, or whether a decrease in the production of both mucin2 and one or more of the trefoil peptides in the presence of said wild-type AGR2 protein is observed upon the addition of said candidate antagonist agent.

203. The method according to claim 200 or 202, wherein the expression of mucin2 and/or the trefoil peptide(s) is determined via quantitative PCT analysis using muc2- and trefoil peptide-specific primers.

204. The method according to any one of claims 192 to 203, wherein said mammalian goblet cells are LS174T or HT29 cells.

205. The method according to any one of claims 192 to 204, wherein the candidate agent is selected from the group consisting of

a) a peptide or polypeptide;

b) a nucleic acid (including a peptide nucleic acid); and

c) a small molecule having a molecular weight of no more than 2000 Dalton, preferably no more than 1500 Dalton, more preferably no more than 1000 Dalton, and most preferably no more than 500, 400, 300, or even 200 Dalton.

206. An agent identified or identifiable by a method according to any one of claims 192 to 205.

207. Use of an agent according to claim 206 for the prevention, amelioration, or treatment of a medical condition associated with an alteration in goblet cell function.